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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
KUBELIK, ANNE R	

ART UNIT	PAPER NUMBER
1638	

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10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/882,434	MANNERS ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *3 and 4* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 5-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *with the application* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/117615* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of Group I (claims 1-2 and 5-15) in Paper No. 9, filed 30 December 2002 is acknowledged. The traversal is on the ground(s) that claims 1 and 5 and claims 1 and 14 are linking claims that link the wild-type species of group I and the mutant species of group II. Applicant urges that upon allowance of linking claims 1 and 5 and/or 14, the restriction should be withdrawn.

This is not found persuasive because each nucleotide sequence requires an independent search of the databases. A search on a nucleic acid encoding SEQ ID NO:1 will not find art on a nucleic acid encoding a variant of SEQ ID NO:1; a nucleic acid encoding such a variant requires a separate search. Thus, the searches for Group I and Group II are independent and non-overlapping. Furthermore, there is no genus that encompasses the wild-type DNA and the mutant DNA.

Finally, even if claims 1, 5 and/or 14 are deemed to represent linking claims, a decision on rejoinder will not be made until indication of allowable subject matter. Rejoinder will only be considered if any linking, genus claims are deemed allowable, if all of the claim limitations of the allowable genus claims are in the claims of the nonelected group, and if additional search and consideration is not required for examination of the nonelected group.

The requirement is still deemed proper and is therefore made FINAL. Claims 3-4 are withdrawn from consideration as being drawn to nonelected inventions. Claims 1-2 and 5-15 are examined to the extent they read on wild-type DNA.

2. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows: In the first paragraph of the specification, the

filing date of parent application 09/364,395 is incorrectly given as 30 July 1995. The actual filing date of that application is 30 July 1999. Additionally, International Application No. PCT/AU97/00052 was filed 31 January 1997, not 31 January 1996. See the enclosed copy of the published application.

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825.

Sequence identifiers are required in either the legend or the Brief Description of Figure 6.

Full compliance with the sequence rules is required in response to this Office action. A complete response to this Office action must include both compliance with the sequence rules and a response to the issues set forth below. Failure to fully comply with both of these requirements in the time period set forth in this Office action will be held to be non-responsive.

4. The abstract is not descriptive of the instant invention, which a *Macadamia integrifolia* nucleic acid encoding an anti-microbial protein, constructs comprising the nucleic acid, and cells and plants comprising the constructs. A new abstract is required that is clearly indicative of the invention to which the claims are directed. The abstract of the disclosure should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

5. The title of the invention is not descriptive of the instant invention, as above. A new title is required that is clearly indicative of the invention to which the claims are directed. Note that titles can be up to 500 characters long.

6. The disclosure is objected to because the section title "BEST MODE AND OTHER MODES FOR CARRYING OUT THE INVENTION" on pg 5, line 28, should be replaced with --DETAILED DESCRIPTION OF THE INVENTION--. See MPEP 608.01(a) and (g).

7. The Brief Description of Figure 12 is objected to because the information on pg 30, lines 4-8 should be in that description.

Claim Objections

8. Claims 1-2 and 5-15 are objected to because of the following informalities:

In claims 1 and 14, part (i), "(SEQ ID NO:1)" should be replaced with --SEQ ID NO:1--.

In claim 1, part (ii), claim 5, line 1, and in claim 6, line 1, "includes" should be replaced with --comprises--.

Claims 2, 6-7, 9, 11-13 and 15 lack an article at the start of the claim.

Claims 5, 8 and 10 have an improper article before "DNA" in line 1.

In claim 13, line 3, "soybeans" should be singular to be consistent with the other members of the group.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1, 5 and 7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 7 is directed to specific plasmids pPCV91-MiAMP1 and pET-MiAMP1. Since the plasmids are essential to the claimed invention, they must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. If the plasmids are not so obtainable or available, a deposit of microorganism containing said plasmids may satisfy the requirements of 35 USC 112. The specification does not disclose a repeatable process to obtain the plasmids and it is not apparent if the plasmids are readily available to the public. Thus, a deposit is required for enablement purposes.

If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;
(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;
(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the enforceable life of the patent, whichever is longer;
(d) a test of the viability of the biological material at the time of deposit (see 37 CFR 1.807); and,
(e) the deposit will be replaced if it should ever become inviable.

11. Claims 1, 5 and 7-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid encoding a protein comprising amino acids

27-102 of SEQ ID NO:1, constructs comprising the nucleic acids, and cells, plants and reproductive material comprising the constructs, does not reasonably provide enablement for any nucleic acid encoding a protein comprising amino acids 27-102 of SEQ ID NO:1, encoding a "variant" or "homologue" of that protein, or encoding any *Protoceae* protein that reacts with any antibody to a protein comprising amino acids 27-102 of SEQ ID NO:1, constructs comprising the nucleic acids, and cells, plants and reproductive material comprising the constructs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broadly drawn to any nucleic acid encoding a protein comprising amino acids 27-102 of SEQ ID NO:1, encoding a "variant" or "homologue" of that protein, or encoding any *Protoceae* protein that reacts with any antibody to a protein comprising amino acids 27-102 of SEQ ID NO:1. The claims are also broadly to constructs comprising the nucleic acids, and cells, plants and reproductive material comprising the constructs.

The instant specification, however, only provides guidance for extraction and purification of a basic anti-microbial protein (MiAMP1) from *M. integrifolia* nuts (examples 1 and 3); testing anti-microbial activity of MiAMP1 against a variety of plant pathogens (examples 2 and 4); testing the effect of MiAMP1 on plant cells (example 5), cultured human cells and red blood cells (example 6) to show no toxicity to these cells; SDS-PAGE of MiAMP1 (example 7); mass spectroscopic analysis of MiAMP1 (example 8); amino acid sequencing of MiAMP1 to yield SEQ ID NO:1 (example 9); production of antibodies to MiAMP1 and identification of antigenic ally related proteins from other *Proteaceae*, but not unrelated plants (example 10); cloning a

MiAMP1 cDNA by RACE PCR to yield SEQ ID NO:2 (example 11); transformation of tobacco with a vector comprising the MiAMP1 cDNA (examples 12-13); production of MiAMP1 in *E. coli* (example 14-15); and PCR mutagenesis of SEQ ID NO:2 to yield nucleic acids encoding SEQ ID NOs:15-21, expression of the products in *E. coli*, and testing the antimicrobial activity of the encoded proteins to find all had enhanced activity (example 16).

The instant specification fails to provide guidance for construction or isolation of the nucleic acids encoding a "variant" or "homologue" of protein comprising amino acids 27-102 of SEQ ID NO: or encoding a *Protoceae* protein that reacts with an antibody to a protein comprising amino acids 27-102 of SEQ ID NO:1. For example, exact hybridization or PCR amplification conditions and probes/primers to use in isolation of nucleic acids other than SEQ ID NO:2 are not taught.

The specification, on pg 7, lines 16-20 suggest that substitutions that alter amino acid charge would negatively affect protein activity. However, making "conservative" substitutions (*e.g.*, substituting one polar amino acid for another, or one acidic one for another) that maintain amino acid charge does not produce predictable results. Lazar et al (1988, Mol. Cell. Biol. 8:1247-1252) showed that the "conservative" substitution of glutamic acid for aspartic acid at position 47 reduced biological function of transforming growth factor alpha while "nonconservative" substitutions with alanine or asparagine had no effect (abstract). Similarly, Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577) teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically

reduced enzyme activity (see Table 1). All these mutated proteins, however, would be "variants" or "homologues" of the original protein.

The specification fails to teach that a Greek key ß-barrel makes up the major structural element of MiAMP1 (McManus et al, 1999, J. Mol. Biol. 293:629-638; see pg 632, right column, paragraph 2) and that MiAMP1 mode of action involves interaction with membrane surfaces (pg 634, right column, paragraph 1). Mutations that disrupt this structure would likely destroy the protein's ability to function as an anti-microbial protein. The specification fails to provide guidance for that structure, and thus fails to provide guidance for construction of "variants" and "homologues" within the full scope of the claims.

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate nucleic acids encoding "variants" and "homologues" of SEQ ID NO:1. Making all possible single amino acid substitutions in an 102 amino acid long protein like that encoded by SEQ ID NO:2 would require making and analyzing 19^{102} nucleic acids; these proteins would have 99% identity to SEQ ID NO:1. Because nucleic acids encoding "variants" and "homologues" of SEQ ID NO:1 would encode proteins with many amino acid substitutions, many more than 19^{102} nucleic acids would need to be made and analyzed.

As the specification does not describe the transformation of any plant with a gene encoding a "variant" or "homologue" of SEQ ID NO:1, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims and plants transformed therewith, to identify those with increased disease resistance, if such plants are even obtainable.

Given the claim breath, unpredictability in the art, undue experimentation, and lack of guidance in the specification as discussed above, the instant invention is not enabled throughout the full scope of the claims.

12. Claims 1, 5 and 7-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to any nucleic acid encoding a protein comprising amino acids 27-102 of SEQ ID NO:1, encoding a "variant" or "homologue" of that protein, or encoding any *Protoceae* protein that reacts with any antibody to a protein comprising amino acids 27-102 of SEQ ID NO:1. In contrast, the specification only describes a coding sequence from *M. integrifolia* that comprises SEQ ID NO:2 and variants encoding SEQ ID NOs:15-21. Applicant does not describe other DNA molecules encompassed by the claims, and the structural features that distinguish all such nucleic acids from other nucleic acids are not provided.

Hence, Applicant has not, in fact, described DNA molecules that encode an anti-microbial protein within the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and physical characteristics of the claimed compositions, it is not clear that Applicant was in possession of the genus claimed at the time this application was filed.

See *Univ. of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ 2d 1398 (Fed. Cir. 1997):

> The name cDNA is not in itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical

> characteristics; in other words, it thus does not describe human insulin cDNA .... Accordingly, the specification does not provide a written description of the invention ....

and at pg 1406:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicted, does not suffice to define the genus because it is only an indication of what the genes does, not what it is.

See *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ 2d 1016 at page 1021:

> A gene is a chemical compound, albeit a complex one, and ... conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials .... Conception does not occur unless one has a mental picture of the structure of the chemical or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by it principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 1-2 and 5-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections.

Claims 1 and 14, part (i), are indefinite in their recitation of "an amino acid sequence ...." It is not clear if any number of amino acids of residues 27-102 of SEQ ID NO:1 are contemplated or if Applicant intended that the protein comprise all of amino acids 27-102 of SEQ ID NO:1. If the latter, it is suggested that "an amino acid sequence corresponding to" be deleted.

Claims 1 and 14, part (ii), are indefinite in their recitation of "homologue". The extent to which and nature in which a homologue differs from SEQ ID NO:1 is unclear.

Claims 1 and 14, part (iii), are indefinite in their recitation of "variant". The extent to which and nature in which a variant differs from SEQ ID NO:1 is unclear. The extent to which and nature in which a variant differs from a homologue is also unclear.

Claims 1 and 14, part (iv), are indefinite in their recitation of "specifically reacts" and "essentially the same". It is unclear what kind or extent of reaction is specific. It is also unclear how different the activity of the protein can be and still have "essentially the same" anti-microbial activity.

Claim 5 lacks antecedent basis for the limitation "said encoded protein" in line 2.

Claim 12 is indefinite in its recitation of "forestry". "Forestry" is not plant. It is suggested that the word be replaced with --trees--, if there is support in the specification.

Claims 8 and 10 are indefinite in their recitation of "harbouring". It is not clear if the cell and plant harbor the construct in the sense of protecting it or if Applicant intended that the cell and plant comprise the construct. If the latter, it is suggested that "harbouring" be replaced with --comprising--.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 1, 5, 8-11 and 13-15 rejected under 35 U.S.C. 102(b) as being anticipated by Terras et al (1995, Plant Cell 7:573-588).

Terras et al teach a radish nucleic acid encoding an anti-microbial protein that would be a "variant" or "homologue" of SEQ ID NO:1 (Fig. 5). Terras et al also teach a construct in which the nucleic acid is operatively linked to the enhanced 35S promoter and tobacco plants transformed with the construct (all of pg 579 and Fig. 9A). Seeds would have been produced from the transgenic plants in order to produce the T1 and T2 progeny plants (paragraph spanning the columns, pg 579 and right column, paragraph 3).

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claims 1, 5 and 8-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Terras et al (1995, Plant Cell 7:573-588) in view of Gordon-Kamm et al (1990, Plant Cell 2:603-618).

The claims are drawn to grains, vegetables or oil-seed plants transformed with a nucleic acid encoding an anti-microbial protein that is a "variant" or "homologue" of SEQ ID NO:1.

The teachings of Terras et al are discussed above. The plants produced by Terras et al were resistant to *Alternaria longipes* ((pg 579, right column, paragraph 3). Terras et al do not disclose grains, vegetables or oil-seed plants transformed the nucleic acid.

Gordon-Kamm et al teach transformation of maize, a grain, an oil seed crop and a vegetable (pg 604-605 and 607).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of producing pathogen-resistant plants as taught by Terras et al, to transform the nucleic acid into maize as described in Gordon-Kamm et al. One of ordinary skill in the art would have been motivated to do so because of the economic importance of maize and because of the effectiveness of the nucleic acid when transformed into tobacco.

19. Claims 2 and 6 are free of the prior art, given the failure of the prior art to teach or suggest an isolated nucleic acid comprising nucleotides 70-375 of SEQ ID NO:2.

20. Claims 2 and 6 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, and the objections, both set forth in this Office action, and to include all of the limitations of the base claim and any intervening claims.

Conclusion

21. No claim is allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service at (703) 308-0198.

Anne R. Kubelik, Ph.D.
March 6, 2003